H. Saisho

Endoscopic Retrograde Cholangiopancreatography

Pancreatography was first performed by Pillan in 1909 for the study of autopsy specimens [1]. In clinical use, operative pancreatography was established by Doubilet and Mulholland [2], and Leger [3] early in the 1950s. Endoscopic cannulation and pancreatic duct visualization was first reported by McCune in 1968 [4]. In 1970, Oi [5] and Takagi et al. [6] reported retrograde cholangiography as well as pancreatography with the aid of a flexible duodenoscope. Thereafter, endoscopic retrograde cholangiopancreatography (ERCP) was rapidly established as a diagnostic procedure in practice for the pancreas and biliary tract. With the improvement of the instruments and ancillary devices, it has also evolved to become a therapeutic procedure for the management of various pancreatobiliary disorders.

With the development of newer diagnostic imaging procedures over the last quarter of a century, the diagnostic role of ERCP in clinical practice has changed.

Indications

Less invasive imaging techniques than ERCP, that is ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), have proven useful in the diagnosis of pancreatic diseases. In particular, the development of magnetic resonance cholangiopancreatography (MRCP) in the late 1990s has reduced greatly the need for diagnostic ERCP [7]. However, the precise delineation of duct changes is still the diagnostic priority of ERCP for visualizing small or mild abnormalities, thus leading to an early diagnosis [8]. In addition, brush cytology and forceps biopsy as well as pancreatic juice collection for cytology via ERCP are helpful in establishing a tissue diagnosis.

Pancreatic Malignant Tumors

The diagnosis and staging of pancreatic carcinoma is mostly achieved by the combined use of modern US, CT, and MRI. The need for ERCP may remain only in a small group of special cases such as a small carcinoma undefined on conventional imaging and unusual neoplasms including lymphomas and metastatic cancers, the diagnosis of which is apt to be difficult. The latter may present with a smooth narrowing of the pancreatic duct in a compressed fashion (Fig. 9.1). The nature of the tumor, expansive or invasive, will directly reflect upon the radiological features of the stenotic segment, which will be outlined more precisely with ERCP than with MRCP. When an unusual pancreatic mass is suggested by the first-line imaging, ERCP may provide useful information relating to the nature of the tumor pathology.

Besides the highly detailed findings of the distorted pancreatic ducts, the possibility of tissue sampling at the same time is an additional merit of ERCP. Although the sensitivity of pancreatic carcinoma is 30–50% in brush cytology and forceps biopsy via ERCP [9–11], the validity of tissue diagnosis is basically different from that of imaging diagnosis, having the advantage of providing the final diagnosis. ERCP cytology or biopsy sampling should be an integral part of tissue diagnosis including endoscopic-US-guided fine-needle biopsy sampling and percutaneous CT or US-guided biopsy sampling.

Acute Pancreatitis

ERCP is usually unnecessary or contraindicated in the acute stage of pancreatitis except for the treatment of gallstone pancreatitis. In the convalescence stage, ERCP is useful for establishing the critical causes of pancreatitis, including a small cancer of the papilla (Fig. 9.2) or the pancreas, and biliary microcaluculi. Pancreas divisum, which may cause so-called dorsal pancreatitis, is defined almost only by ERCP.

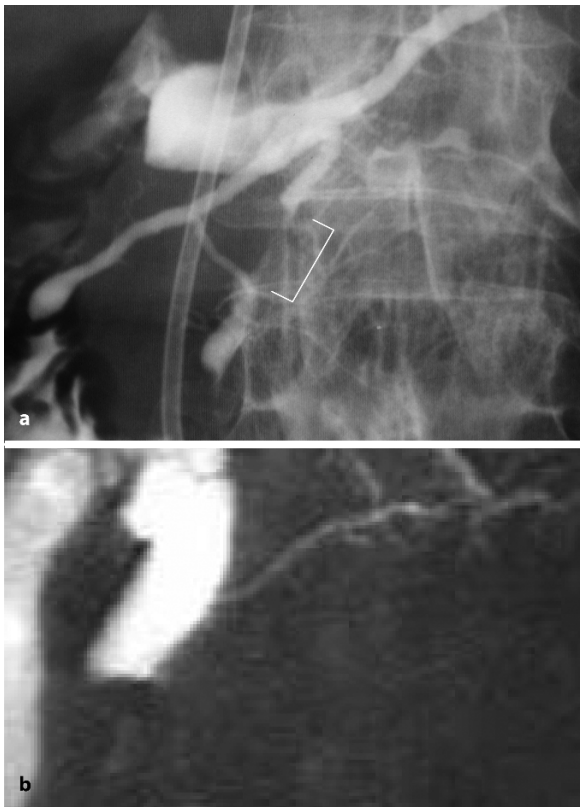

Figure 9.1

a Compressed type of stricture of the main pancreatic duct due to pancreatic malignant lymphoma. Endoscopic retrograde cholangiopancreatography (ERCP) pancreatogram apparently demonstrating a long, smooth, and straightened stenosis (marked with a *white square bracket*) that is a little deviated from the axis of the duct. **b** Magnetic resonance cholangiopancreatography (MRCP) pancreatogram providing no useful information concerning the strictured segment

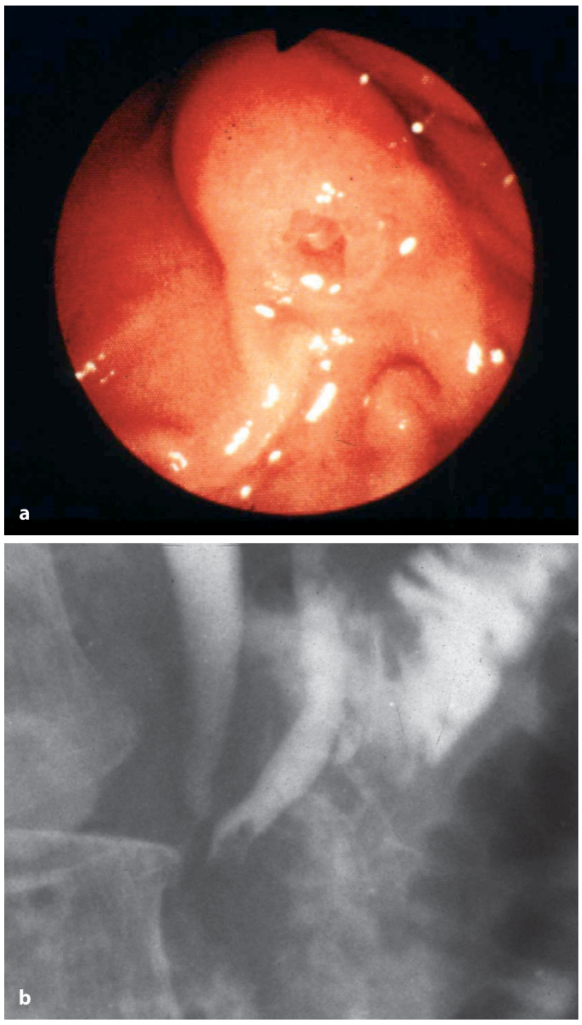

Figure 9.2

A small carcinoma of the papilla of Vater found in a patient with acute pancreatitis. **a** Duodenoscopic view of the swollen papilla of Vater, and **b** a small filling defect in the terminal end of the pancreatic duct revealed with ERCP. The diagnosis of carcinoma was finally proven by biopsy sampling in the orifice of the papilla

Chronic Pancreatitis

Calcified concrements in the pancreas, the specific findings for chronic pancreatitis, can be readily demonstrated by US or CT. The role of ERCP has been reduced in diagnosing calcified chronic pancreatitis. MRCP has been also replacing ERCP for the anatomical evaluation of the pancreaticobiliary system prior to planning of therapy in these patients.

In patients with noncalcified chronic pancreatitis, the delineation of the pancreatic ducts is important for the diagnosis. In the absence of pancreatic calcification, duct-caliber irregularity with stenoses and dilatations is the decisive feature of chronic pancreatitis, typically providing the radiological configuration of so-called "chain of lakes" in the main duct as well as in the side branches (Fig. 9.3). The typical changes can also be defined on MRCP. Therefore, ERCP may be saved for difficult cases undefined on MRCP or considered to benefit from qualified duct visualization.

The details of a diffuse or a long irregular narrowing of the pancreatic ducts in autoimmune pancreatitis is mostly defined by ERCP (Fig. 9.4). Brush cytology and forceps biopsy sampling via ERCP may be helpful in diagnosing tumefactive pancreatitis, which is often mistaken for a malignancy.

When the irregularities are presented solely in the side branches, interpretation of the pancreatogram is

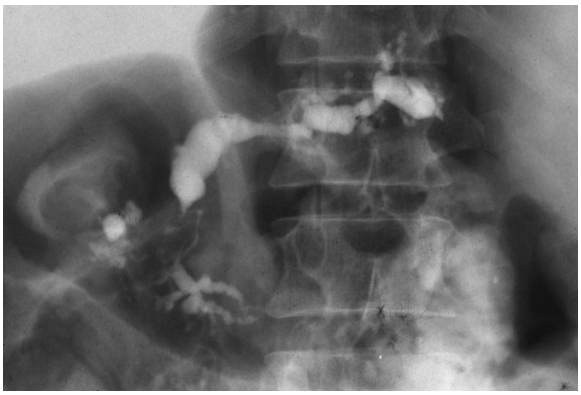

Figure 9.3

ERCP pancreatogram demonstrating multiple stenoses and alternating duct dilatations, a typical configuration of a duct–caliber irregularity in noncalcified chronic pancreatitis

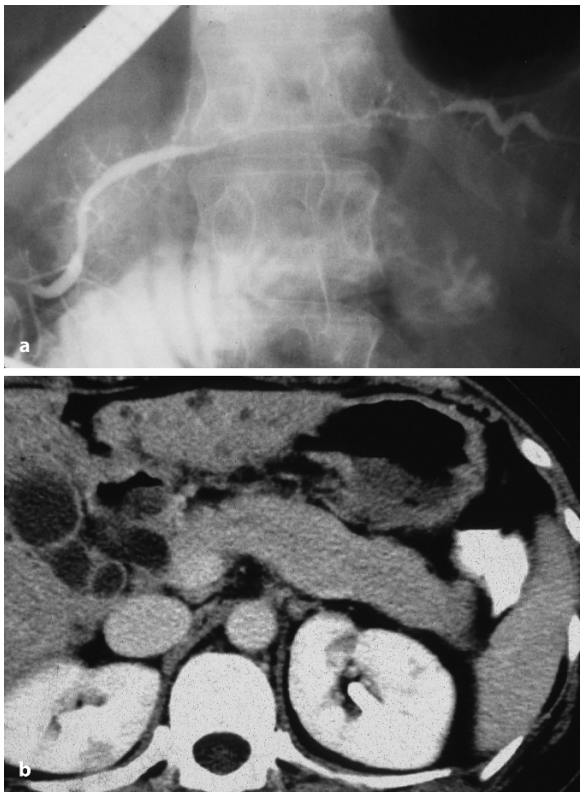

Figure 9.4

Autoimmune pancreatitis. **a** The characteristic long, irregular narrowing of the main pancreatic duct demonstrated with ERCP. **b** The enlarged pancreas revealed by computed tomography (CT) images

challenging to the clinician, for these may be found not only in patients with mild pancreatitis, but also in aged people. While up to now the detection of duct branch abnormalities in ERCP are the diagnostic mainstay at an early stage of pancreatitis or mild pancreatitis, these abnormalities are not always pathognomonic in the patients with no pancreatitic symptoms or no history of previous pancreatitis [12].

Few patients had "actual" chronic pancreatitis that could not have been excluded by using other imaging techniques and laboratory work-up. Based on these considerations, diagnostic ERCP is of almost no use for patients with abdominal pain of possible pancreatic or biliary origin, when there are no other objective findings on the biliopancreatic system [13, 14].

Instruments and Accessories for ERCP

Side-viewing video endoscopes with standard 3.2- to large 4.2-mm channels are now the most commonly used. Smaller duodenoscopes are available for examination in neonates and small children. However, the standard endoscope may be used in children over the age of 2 years. A variety of 4-Fr to 6-Fr cannulae are available for intubation and contrast injection into the pancreatic and bile ducts. Brushing catheter and biopsy forceps should be prepared for use as necessary. It is also desirable to have plastic stents or drainage tubes (of 7 or 8 Fr) near at hand for unexpected cases requiring postprocedural duct decompression.

Preoperative Preparation

Disinfection of Instruments

Immediately before the procedure, it is necessary to ensure that the instruments and accessories to be used are clean and sterile. As for the accessories including cannulae, catheters, guide wires, and sampling forceps, disposable devices provided in a sterile state are available and recommended for use for the prevention of cross-infection.

The endoscope should be reprocessed at high standards of disinfection according to accepted protocols and guidelines [15, 16]. In endoscope reprocessing, the cleaning (including brushing and flushing the working and air/water channels) immediately after use is generally the critical step for the removal of blood, secretions, or other debris. Then, after rinsing under running water, disinfection of the endoscope is automatically processed in a disinfection system with

a disinfectant solution by following the manufacturer's instructions. In addition to final rinsing, it is necessary to assure correct drying to prevent recontamination of microorganisms during storage.

Patient Preparation

The procedure is performed in the morning after overnight fasting, or when the patient is fasted for at least 6 h prior to the procedure. Lidocaine (Xylocaine) in solution or spray is used for topical pharyngeal anesthesia and any one of the sedatives including diazepam (Valium, Cercine, or Horizone), midazolam (Dormicum), petidine hydrochloride (Opystan), and meperidine hydrochloride (Demerol) is usually given intravenously immediately before the endoscope insertion. Glucagon (0.25–0.5 mg) or Buscopan (20–40 mg) is administered also intravenously to relax the duodenum and to facilitate cannulation.

Prophylactic Use of Antibiotics

Antibiotic prophylaxis is recommended in patients with the high-risk factors described below. Infection of the biliopancreatic system is one of major complications following ERCP. It has been well known that biliary obstruction, a history of previous cholangitis, and pancreatic pseudocyst are the main risk factors for infection. Cholangitis and sepsis are common after ERCP, when the establishment of biliary drainage is incomplete in patients with a biliary obstruction [17, 18]. The pathogens are mainly enteric Gram-negative microorganisms such as *Escherichia coli*, *Klebsiella* spp., and *Enterococcus* spp. [19]. In patients with any one of the risk factors, prophylactic administration of a broad-spectrum antibiotic covering these Gram-negative bacteria is recommended just before the procedure [20]. The addition of antibiotics to the contrast medium may be of no use [21].

Bacterial endocarditis is another potential infection following ERCP, as well as the other upper gastrointestinal endoscopy. Patients at high risk who have heart valve disorders, prosthetic heart valves, and also major vascular disorders including recent (<1 year) synthetic vascular graft placement should be considered for antibiotic prophylaxis. As mentioned elsewhere in authorized guidelines [20, 21], the regimens are important to cover streptcocci and staphylococci, which are the most common pathogens of endocarditis. Otherwise, general use of prophylactic antibiotics is considered unnecessary.

Major Points of the ERCP Technique

The patient is placed prone or in a left lateral decubitus position on a fluoroscopic table. The duodenoscope used in ERCP is a side-viewing instrument, which requires some skill for the operator at several points during the passage through the esophagogastric canal into the descending duodenum. The cannulation of the papilla also requires other delicate techniques critical for ERCP.

Passage of the Esophagogastric Junction into the Stomach

A side-viewing duodenoscope is gently passed through the oropharynx into the esophagus in the angle-free maneuver; sometimes, a brief use of the right-left angle lock may be better to pass the esophageal entrance. While it is slowly advanced into the stomach almost blindly, there may be a resistance on the terminal end of the esophagus. To pass this part smoothly, a bit of a rotating maneuver over the instrument shaft is helpful. When the tip of the instrument comes into the stomach, an adequate amount of air is insufflated to secure the view. Sometimes, the tip of the scope may be trapped in the fundus, curling up in reverse. To avoid this problem, after passing the cardiac entrance, the instrument is rotated counterclockwise to get the view of the longitudinal folds in the greater curvature. Then, it is so advanced as that the tip comes in touch on the folds and rotated clockwise so as to obtain a view of the lesser curvature and the gastric angle downward. Thereafter, with bending the tip slightly upward, it is pushed forwards under visual control until it reaches the pyloric antrum.

Passage of the Pylorus

As the pylorus is approached, it sinks down to the middle of the bottom of view. As the tip of the instrument is further advanced, the view is obstructed in a moment, immediately before it flips into the duodenal bulb. If the view is still obstructed in spite of a pushing maneuver, the instrument is withdrawn to make the second attempt with a corrected adjustment for the direction.

Insertion into the Descending Duodenum

In the duodenal bulb, the tip is bent downward and the instrument is withdrawn a little to detect the superior duodenal angle in the posterior wall, the entrance of the descending duodenum. After the tip is located on this angle, it is intensely bent upward and the entire instrument is rotated clockwise so as to look down the descending duodenum, when necessary, with the help of right angling manipulation. The angling knobs are locked to keep the tip bending as it is, and the "straightening maneuver" is usually performed by pulling the instrument back while applying further clockwise rotation. While any redundant loops of the instrument are straightened in the stomach, paradoxically the tip advances further into the descending part of the duodenum.

When the "straightening maneuver" is not performed well, or afterwards the positioning of the papilla is not appropriate for cannulation, the "pushing maneuver" is an alternative; after the instrument reaches the spot where the descending duodenum is looked down, it is cautiously pushed further into the loop with counterclockwise rotation under visual control. The "pushing maneuver" is often useful for cannulating the minor papilla.

Discovery of the Papilla

When the "straightening maneuver" is completed, the tip has usually advanced distally farther than the papilla of Vater. The bending tip is relaxed, and in withdrawing the instrument slowly, careful observation on the medial wall usually reveals a longitudinal fold and the papilla at the proximal end of this fold.

Cannulation of the Papilla

After the papilla is identified, appropriate repositioning of the instrumental tip is attempted prior to cannulation to get a good face-on view of the papilla in a small look-up position. The positioning is critical to obtain a successful cannulation into the biliary or pancreatic duct.

Contrast Injection

The cannula is brought into view and filled with contrast material. The cannula tip is then carefully advanced and guided into the orifice of the papilla by pressure on the forceps elevator together with attempts to advance the cannula. After the cannula is inserted 5 mm to 2 cm into the papilla, contrast medium is slowly injected under fluoroscopic control. The pancreatic duct is usually outlined first. Sometimes, both the biliary and pancreatic ducts are visualized. To obtain the selective visualization of either one, a deep cannulation into the target duct is required by more careful maneuvering of the cannula tip aligned along the axis of the target duct. In general, cannulation rightwards to the long axis of the duodenum favors the pancreatic duct, whilst upwards angulation favors the bile duct.

Technical Aspects for Radiography

With regard to the gravitational effect, the left lateral position is adequate to facilitate filling of contrast medium in the pancreatic duct system, which runs from right to left across the body. The filling of contrast medium is controlled under television fluoroscopic observation. Overfilling of the pancreatic ducts must be avoided by careful injection of contrast medium.

Although filling of the small branches may not be recognized on the television monitoring screen, they are usually visualized on x-ray films when the whole figure of main pancreatic duct (MPD) is seen clearly on the screen. Excessive contrast medium overfills the duct system, resulting in "acinar filling," which may cause acute pancreatitis.

When the duct systems are filled enough, radiograms are taken after changing the patient's position to the prone or supine, as the lateral radiogram gives a less clear view. If an abnormal finding is noticed, additional films are taken at the proper positions so as to reveal the significant area without superimposing the instrument, the spine, and the contrast medium that has leaked into the intestine.

Then, the cannula and the scope are withdrawn and radiograms are again taken in various projections. At this time, the radiograms can exhibit the natural course and location of the duct systems. The contrast medium in the duct systems is drained through the papilla. The normal pancreatic duct system is completely cleared within a few minutes. Cysts or localized dilatations become more noticeable due to the retained contrast medium.

Interpretation of the Pancreatogram

Normal Pancreatogram

The pancreas is transversely located in the retroperitoneal space between T12 and L2, lying over the spine and aorta. The MPD, which is usually drained by the duct of Wirsung, runs up from the major papilla in the head, and angles to the left so as to run across the spine and slightly cranially in the tail up to the splenic hilum. The duct contour is smooth and gradually tapering toward the tail, diverging into branches to disappear within the tail tip. The maximum diameter, approximately 4 mm on average, is found in the head, while the caliber tends to increase in advancing age [22]. The accessory duct (the duct of Santorini) is found in about 80% of people. This communicates with the MPD in the neck of the pancreas, the transitional zone of the head to the body, and runs to the minor duodenal papilla, situated about 2 cm oroventrally to the major papilla. Many branch ducts join the MPD at right angles to the MPD except in the head, where they are larger and less numerous. The largest one in the head drains the uncinate process. The branch ducts are usually visualized less clearly in the body than in other parts.

Pancreas divisum, in which pancreatic drainage is mainly through the minor papilla, has been reported in 3–9% of autopsy and ERCP series [1, 23, 24]. In our ERCP experience in Japan [22], it was found in only 20 (1.6%) of 1263 patients having no pancreatic diseases, and among them only 8 patients (0.6%) had complete divisum in which the small duct Wirsung was isolated from the main drainage (the duct of Santorini) and terminated into a fine network within the head of the pancreas.

Abnormal Pancreatogram

Ductal Stenosis or Obstruction

Ductal stenosis or obstruction is an essential finding in either neoplasms or inflammatory processes of the pancreas. An isolated stenosis with upstream dilatation is usually indicative of pancreatic carcinoma. Duct obstruction, or contrast stop, is also usually due to tumors. In particular, the "double duct stricture" sign, concurrent obstruction at the same level in the common bile duct and MPD, is almost specific to carcinoma of the pancreas head [25] (Fig. 9.5). However, some inflammatory processes may present with a stenosis or an obstruction that mimics those found in patients with pancreatic carcinoma. Endoscopic brush cytology or forceps biopsy sampling via the papilla may be considered to obtain a definite diagnosis for the selected patients when the pancreatograms are confusing.

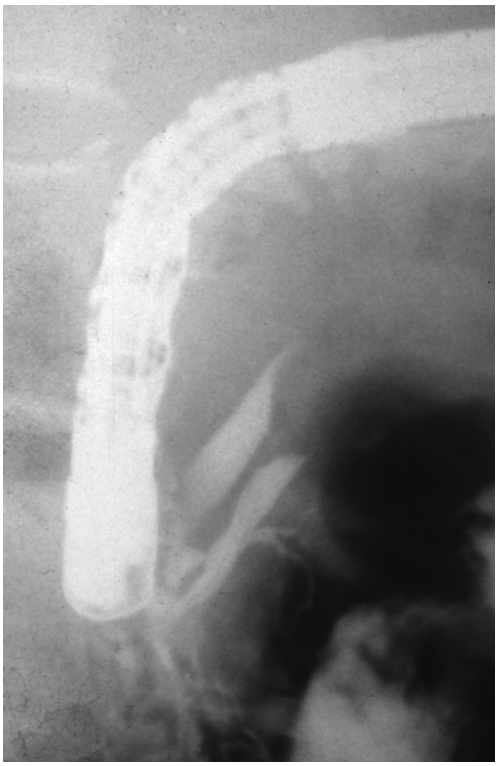

Figure 9.5

ERCP pancreatogram demonstrating the "double- duct stricture" sign due to carcinoma of the pancreas head

Variations of Caliber

The duct configuration of multiple stenoses and alternating segmental dilatations, well noted as irregular dilatations, is characteristic for advanced chronic pancreatitis. It is frequently associated with contrast defects due to pancreatic stones. The variation in caliber may reflect the irregular distribution of inflammatory and fibrotic processes in the pancreas.

Irregular Narrowing of the MPD

Diffuse or elongated irregular narrowing of the MPD with or without a mild dilatation upstream is found in another type of chronic pancreatitis or autoimmune pancreatitis [26, 27]. In this type of pancreatitis, a focal or global enlargement of the pancreas is usually revealed on medical imaging, and this is challenging

Figure 9.6

Tumefactive pancreatitis (autoimmune pancreatitis). **a** ERCP pancreatogram demonstrating a long, irregular narrowing of the main duct in the head with a moderate dilatation accompanied in the upstream. **b** A focal enlargement of the corresponding site of the pancreas seen in CT images may be confusing to exclude a malignancy

for differentiation from a neoplastic tumor [28]. Even though the duct configuration seems a little bit different from the typical stricture in the case of carcinoma, brush cytology is helpful to solve the problem (Fig. 9.6).

Dilatation of the Pancreatic Ducts

Marked dilatation of the pancreatic ducts with an intraductal mucinous substance is indicative of intraductal papillary mucinous neoplasm (IPMN). When the neoplasm originates in the branch ducts, cystic dilatations in the branches may be found. However, the entire visualization of the pancreatic duct system is usually blocked by the massive amounts of mucin that fill the ducts (Fig. 9.7). MRCP is the tool of choice to display the entire pancreatic duct system in patients with IPMN. Observation of mucinous substance and pancreatic juice sampling for cytology during ERCP is helpful in the diagnosis [11].

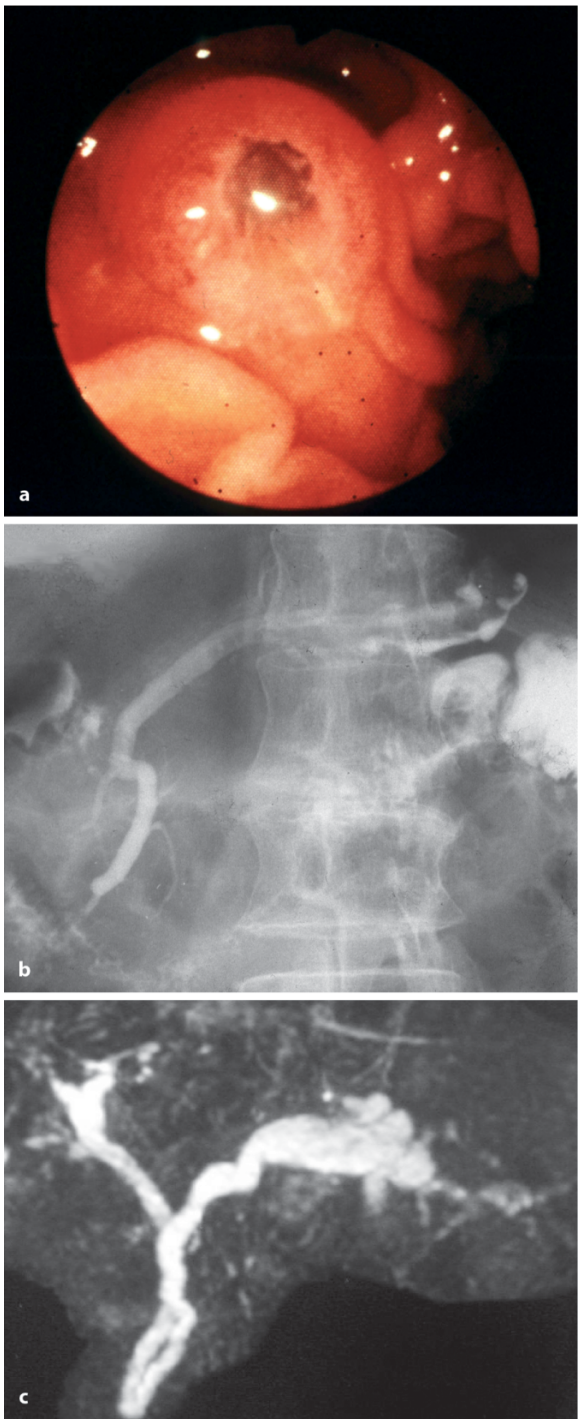

Figure 9.7

Intraductal papillary mucinous neoplasm. **a** Mucinous substance choked in the loose orifice of the papilla of Vater found on the endoscopic observation is a strong clue for the diagnosis. However, the complete duct delineation is impossible with ERCP due to excessive mucinous substance filled in the ducts (**b**). **c** MRCP is better for examining the whole profile of the duct system

Minimal Abnormalities of the Pancreatic Ducts

Minimal abnormalities of the pancreatic ducts such as mild dilatation, low-grade irregularities, and side-branch abnormalities may be found in patients with an early tumor or mild pancreatitis. These mild changes are also seen in aged people at times, and then, the interpretation is an intricate issue in practice. However, the detection of mild duct changes could be the first step for the early diagnosis. In spite of the great progress in modern diagnostic imaging, ERCP remains a mandatory tool because of the high-quality and accurate visualization of the pancreatic ducts.

Complications and Prophylactic Therapy

ERCP is a relatively safe procedure; however, it is always accompanied by the potential risk of complications common to other types of gastrointestinal endoscopy and those peculiar to this procedure. Among the latter complications, pancreatitis and infections are noteworthy and important from the clinical viewpoint.

Post-ERCP Pancreatitis

Pancreatitis is the most frequent complication of ERCP: post-ERCP pancreatitis occurs in 1–7% of cases [17, 18, 29–31] The variation in frequency is thought to be correlated with differences in the definition of post-ERCP pancreatitis, the demography of subjects, and/or ERCP techniques used. The definition of post-ERCP pancreatitis has a consensus as follows: new or worsened abdominal pain with a serum amylase three or more times the upper limits of normal 24 h after the procedure, requiring at least 2 days of hospitalization [32].

The incidence of pancreatitis may be related to the proportion of patients with a high risk for the complication. The patient-related risk factors for pancreatitis have been studied and are now well established [33]. These include young age, female gender, a history of recurrent or post-ERCP pancreatitis, and sphincter of Oddi dysfunction. The frequency of pancreatitis is reported to increase to 40% in patients with multiple risk factors [34].

Technique-related risk factors are also important. The rate of complication probably relates to the endoscopist's level of expertise. In particular, papillary trauma due to repeated attempts at cannulation will cause pancreatitis. Other possible factors include the repeated contrast injection into the pancreatic ducts and the excessive contrast injection at a high pressure. However, pancreatic parenchymal acinarization due to an over-pressured injection of contrast has been recently thought less harmful than considered previously [29, 20, 33].

Prevention of post-ERCP pancreatitis is an important issue in practice. The prophylactic use of pharmacological agents that may prevent pancreatitis is attractive for the selected high-risk patient, because post-ERCP pancreatitis is not predictable for each patient before the procedure. So far, preoperative administration of somatostatin, octreotide, corticosteroids, glycerol trinitrate, heparin, and gabexate mesilate have been attempted with a view to prevention of the complication. Among these agents, somatostatin (a suppressor of pancreatic exocrine secretion) and gabexate (a protease inhibitor) are suggested to be effective in several randomized controlled studies [35–39], but their use has not yet been put into widespread clinical practice. The routine use of these agents is not cost-effective because a considerable number of patients should be treated for one patient's benefit. Randomized controlled trials in the selected subjects with high-risk of post-ERCP pancreatitis are awaited to show a clinical and cost benefit in the prophylactic use of these agents.

Placement of a pancreatic stent is an option with demonstrated efficacy for the prevention of post-ERCP pancreatitis in high-risk patients, particularly for suspected sphincter Oddi dysfunction [40, 41]. However, this method has its own limitation: stent placement following the ERCP procedure would be difficult. In fact, failure rates after biliary intervention ranged from 5% to 10%. Furthermore, failure of stent placement is associated with a high incidence of pancreatitis [42].

Cholangitis and Sepsis

Infectious complication following ERCP is commonly observed in association with incomplete biliary drainage. Two pathways could be attributable to developing the processes: infection of the pancreaticobiliary system by contaminated instrumentation, or invasive spread of already existing intraductal organisms due to ERCP manipulation and contrast injection. The establishment of adequate pancreaticobiliary drainage immediately after ERCP is recognized as the most important way of preventing infective complications. Antibiotics should be used in patients with known cholangitis. In addition, use of postprocedural antibi-

otics may reduce infectious complications in patients with incomplete biliopancreatic drainage and unexpected filling of pancreatic pseudocysts [19]. But the routine use of prophylactic antibiotics does not appear to reduce this risk and is not recommended [43]. Infection of *Pseudomonas aeruginosa* is rare, but when it is found, incomplete disinfection of the instruments should be considered [44].

Prophylactic antibiotics should be also recommended for patients with heart-valve disorders, prosthetic heart valves, a prior history of endocarditis, systemic-pulmonary shunt, or recent (<1 year) synthetic graft placement [20, 21]. Nonetheless, better skills and experiences of endoscopists and other medical staff can decrease the frequency of complications associated with ERCP. Endoscopists and staff should receive adequate training and ensure that they are exposed to a sufficient case volume to warrant providing this procedure.

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